altered in Alzheimer's disease thus providing a basis for an assay for the disease. Furthermore, from work leading up to the present assay, an improved means of treating Alzheimer's disease has been discovered based on modulating the interaction between divalent cations and/or heparin and APP.

C1 Cont

Please delete the paragraph beginning on page 7 and ending at the second line of page 8 and replace with the following:

By modulating the levels of divalent cations or heparin or any other moiety which can bind the heparin binding sites on APP (residues 318-331 and around residues 98-105) or any other binding site on APP capable of binding these moieties (such as additional zinc or heparin binding sites on APP), the range, type and/or extent of APP cleavage can be altered such that incorrect protease-mediated processing of APP can be reduced or inhibited. By "modulate" is meant the alteration of the availability of divalent cations and trivalent cations or heparin or any other moiety which can bind the heparin binding sites on APP (residues 318-331 and around residues 98-105) or any other binding site on APP capable of binding these moieties (such as additional zinc or heparin binding sites on APP) to bind to APP prior to or simultaneously with APPase-mediated cleavage. It has been found that zinc (Zn^{2+}) binds to APP at a specific and saturable binding site. The zinc binding site on APP was identified by enzymatic digestion of purified APP695-fusion protein coupled to Zn^{2+} -chelating sepharose. The synthetic peptide representing about residues 181-200 of APP, situated between the cysteine rich and negatively charged domains of the protein, was shown to bind zinc in a specific and saturable manner. The intimate involvement between APP and zinc is strongly suggestive of a role of zinc in APP processing: APP binds heparin (in a

C2

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manner analogous to FGF). Heparin has been shown to protect APP from proteolytic digestion, as exemplified using the proteolytic enzyme trypsin. Heparin concentration as low as 100 nM cause a marked reduction in the rate and degree of brain APP degradation by trypsin. The brain contains a number of heparin or heparin sulphate containing proteins and thus the interaction of heparin with APP may stabilise APP from proteolytic degradation in-vivo. It has also been found that zinc affects the kinetics of heparin binding to APP, and may increase APP affinity for heparin 5 to 10 fold. Surprisingly, at low zinc concentrations (above about 1 μM) the protective effects of heparin are abolished. This finding indicates that aberrant zinc levels in-vivo, in the brain intracellular and/or extracellular milieu, may promote aberrant APP proteolytic processing giving rise to the amyloid protein, and subsequently Alzheimer's disease and other disorders associated with amyloid deposition in the brain.

c2 Cont

Please delete the third full paragraph on page 12 and replace with the following:

BRIEF DESCRIPTION OF THE DRAWINGS

c3

FIGURE 1 is a photographic representation showing immunoblots comparing Alzheimer's disease and age matched control plasma APP. Plasma heparin-Sepharose eluates (65 μg) were analysed by 8.5% (w/v) SDS polyacrylamide gel electrophoresis and immunoblotting with MAb 22C11 which recognises an amino-terminal epitope (see Example 1). The relative molecular mass of standard protein markers (Rainbow Standards, Amersham, UK) are shown on the left. APP immunoreactive bands of 130, 110 (a doublet), 65 and 42 kDa are indicated by arrows to the right. Only the relative abundances of the 130 and 42 kDa APP forms, as in the sample illustrated, could visibly

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C3 Cont

discriminate between Alzheimer's disease compared to (Figure 1A) non-demented elderly controls and (Figure 1B) normal young control populations.

Please delete the last full paragraph bridging pages 32 and 33 and replace with the following:

EXAMPLE 6

ADMINISTRATION OF ZINC IN ALZHEIMER'S DISEASE (AD)

The subjects from Example 3 were studied.

The healthy volunteers suffered no ill effects from the zinc supplementation.

The two AD volunteers became acutely unwell while on zinc supplementation.

C4

They both suffered a severe loss of cognitive function with mini-mental state examination (Folstein et al., 1975) scores deteriorating from moderately demented levels to unrecordable. Eye movement abnormalities and general levels of self care worsened over the period of supplementation. This response was consistent with a neurotoxic response to the zinc supplementation. When zinc supplementation was ceased, cognitive function returned to the previous levels within two weeks.

IN THE CLAIMS

Please cancel claim 27 without prejudice or disclaimer.

Please substitute claims 28 and 30 below for pending claims 28 and 30:

C5

28. (amended) A method for treating Alzheimer's disease in a patient comprising the step of subjecting said patient to a therapeutically effective amount of an agent which is capable of crossing the blood brain barrier, wherein said agent modulates the interaction within the central nervous system between a divalent or trivalent cation

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